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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/576,785	04/21/2006	Tao Cheng	060230PCTUS	5925

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EXAMINER	
FORD, ALLISON M	
ART UNIT	PAPER NUMBER
1651	
MAIL DATE	DELIVERY MODE
10/23/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/576,785	CHENG, TAO	
	Examiner	Art Unit	
	ALLISON M. FORD	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 June 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *10-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9* is/are rejected.

7)☒ Claim(s) *6* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 April 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *20060830*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group I, claims 1-9, in the reply filed on 6/27/08 is acknowledged.

Claims 1-22 remain pending in the current application, of which claims 10-22 are withdrawn pursuant to 37 CFR 1.142(b) as being directed to non-elected inventions.

Priority

The instant application is a national stage entry under 35 USC 371, of international application PCT/US04/35220, filed 10/25/2004. Acknowledgement is further made of the international application claiming priority to US provisional applications 60/514,329, filed 10/23/2003, and 60/620,154, filed 10/19/2004. Reference to the prior filed US applications is made in the first line of the specification (per amendment of 4/21/2006).

Claim Objections

Claim 6 is objected to because of a minor informality: There appears to be a typographical error in claim 6, "timplant" should be "implant". Correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-9 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant claims are directed to a method comprising controlling the self-renewal of a population of human-compatible stem cells in an intracellular environment substantially free of p18.

The specification does support a correlation between decreased intracellular p18 levels and increased self-renewal of hematopoietic stem cells (evidenced by increased symmetric division in $p18^{-/-}$ hematopoietic stem cells versus $p18^{+/+}$ hematopoietic stem cells). However the only discussion of *how* to control the p18 level in the cells is at page 24 of the specification, wherein Applicant states: "One may control the intracellular environment by, for example, limiting expression of the p18 protein; this may be done by deleting or mutating the p18 gene (to make a p18 -/- genotype cell) or its promoter (to make a p18- phenotype cell), or by down-regulating the gene promoter, or by providing a compound capable of binding and thus neutralizing the p18 protein." Applicant suggests use of siRNA molecules to down-regulate the gene expression, but fails to provide any disclosure of any specific siRNA molecules known to down-regulate p18 gene expression.

Therefore, while the specification appears to suggest use of compounds to down-regulate p18 protein expression, the specification fails to provide disclosure of any specific compound which may be used to achieve such a down-regulation of protein expression. Therefore, written description for the method is lacking because Applicant has not provided sufficient written description of the compounds which are necessary for the method.

Holding of a lack of written description over method claims, wherein compound(s) critical to the method are not fully described, fins basis in the Federal Circuit court decision of *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 927, 69 USPQ2d 1886, 1894-95 (Fed. Cir. 2004). In *University of*

Rochester, the patent at issue claimed a method of selectively inhibiting PGHS-2 activity by administering a non-steroidal compound that selectively inhibits activity of the PGHS-2 gene product. However, the patent did not disclose any compounds that could be used in the claimed methods. While there was a description of assays for screening compounds to identify those that inhibit the expression or activity of the PGHS-2 gene product, there was no disclosure of which peptides, polynucleotides, and small organic molecules selectively inhibit PGHS-2. The court held that "[w]without such disclosure, the claimed methods cannot be said to have been described."). See M.P.E.P. § 2163.

The fact pattern in *University of Rochester* is near identical to the issues in the current application, as the method requires use of a compound to regulate p18 protein expression in cells, but compounds which may effectively regulate the protein expression are not disclosed; thus the holding of lack of written description over the method claims is deemed proper.

Claims 1-9 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Analysis of whether a particular claim is supported by the disclosure in an application requires a determination of whether that disclosure, when filed, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention without undue or unreasonable experimentation. See *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916). The key word is 'undue,' not experimentation.' " (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or

direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The instant claims are directed to a method comprising controlling the self-renewal of a population of human-compatible stem cells in an intracellular environment substantially free of p18. The claims fail to set forth any particular method steps which may be carried out to achieve the desired 'control of self-renewal'. In looking to the specification at page 24, Applicant discusses that the 'controlling' may be achieved by any means which would modulate the expression of the p18 protein in cells. Abstract examples of gene and/or gene promoter deletion, use of enzymes to decrease the proteins, or use of siRNA are disclosed, but no specific examples of particular compounds or methods are provided.

In order to successfully carry out the instant invention, one would need to unequivocally determine the precise role of p18 in hematopoietic stem cell differentiation, determine means to modulate the level of p18 protein in hematopoietic stem cells, and determine threshold levels of the p18 protein expression which must be obtained in order to successfully promote reliable self-renewal of the stem cells.

With regards to teaching and guidance provided in the specification, the experiments are limited to the self-renewal capacity of $p18^{-/-}$ versus $p18^{+/+}$ hematopoietic stem cells obtained from cross-bred mice. There are no examples, actual or prophetic, which manipulate the level of intracellular p18 in stem cell.

With regards to the state of the art, expression of INKC4 gene p18 was recognized as playing a role in hematopoietic stem cell differentiation and self-renewal (See Tschan et al, Br J Hematol, 1999). Tschan et al hypothesize INKC4 cyclin kinase dependent inhibitors, including p18 and p19, play a role

early in the cell cycle, which may affect the cells' ultimate fate to differentiate or self-renew. Tschan et al also suggest p18 and p19 as potential targets for therapies in AML. However, the prior art does not teach any means of modulating the level of p18 in a stem cell.

Though the level of skill in the art of stem cell biology is extremely high, it is submitted that based on the limited information available in the field directed specifically to the role of p18 in hematopoietic stem cell differentiation, and the absence of any specific teaching or guidance in the instant disclosure regarding specific means to control the level of p18 protein expression in HSCs, one would have to undertake an undue amount of experimentation to successfully carry out the claimed invention. Accordingly, claims 1-9 are deemed properly rejected.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-9 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: what is actually being done to control self-renewal of the stem cells. Applicant's claim 1 is directed to a method comprising controlling the self-renewal of a population of human-compatible stem cells in an intracellular environment substantially free of p18, but none of the claims actually recite a positive action which is applied to the stem cells to control the self-renewal of the cells.

Claims 5-9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 5-9 depend from claim 1, which is directed to a method of controlling the self-renewal of a population of stem cells, claims 5-9 require the self-renewal to occur, at least in part, in a human. Claim 6 specifically states the self-renewal of said population in a human comprises implanting in said human a stem cell implant therapeutic for said human.

It is not clear how claims 5-9 relate to the method of controlling the self-renewal of stem cells, as required by claim 1, it is not clear self-renewal is controlled merely by being present in a human, or if additional actions are required. Furthermore, in claim 6, it is unclear how the stem cell implant must be therapeutic for the human, *i.e.* must the stem cell, per se, be therapeutic? must the implantation be part of a therapeutic treatment process? Clarification is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2 and 4 are rejected under 35 U.S.C. 102(b) as being anticipated by Sherr et al (US Patent 6,033,847).

Sherr et al disclose controlling InkK4c-p18 (p18) expression in cells to control cell growth. Particularly disclosed is blocking p18 expression in hematopoietic stem cells (HSCs) to induce the HSCs to enter a proliferative state. The p18 expression may be blocked through use of antisense oligonucleotides that contain nucleotide sequences complementary to nucleic acids that encode p18 polypeptide sequences or through use of antibody compositions that bind specifically to p18 proteins (See Sherr et al col. 5, ln 11-39).

The method of Sherr et al, particularly the embodiment wherein p18 expression is blocked in HSCs is considered to read on the method of the instant claims. HSCs are considered to read on human-compatible stem cells in accordance with the definition in the instant specification (Pg 24, ln 8-14), which defines "human compatible" to mean able to be survivably implanted in a human. The definition permits use of immunosuppressants, thus any cell may be considered human compatible, as the human immune system may be completely suppressed to permit survival of the implanted cell. HSCs are considered undifferentiated stem cells, as they are, by definition, not terminally differentiated. Sherr et al states the level of p18 protein in the cells of their invention is less than that of wild-type, or non-treated, cells. Therefore the reference anticipates the claimed subject matter.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ALLISON M. FORD whose telephone number is (571)272-2936. The examiner can normally be reached on 8:00-6 M-Th.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Allison M. Ford/
Examiner, Art Unit 1651